Example 1, Applicants discovered that PIK3CA is amplified in ovarian cancer and further, that PIK3CA is overexpressed in ovarian cancer (Example 2, page 30). Applicants also showed that ovarian cancer cells with increased PIK3CA expression also exhibited increased PI kinase activity (Figure 3), and lastly, that a specific inhibitor of PI kinase, inhibited ovarian cancer cell proliferation. In light of these observations, the inventors recognized that inhibition of PI kinase would have therapeutic benefits. As PI kinases are well studied and inhibitors of these enzymes are known, the inventors recognized that any of a number of means of inhibiting the activity of PI kinase could be used in the invention. Claims 37-39 are therefore directed to methods of inhibiting the proliferation of ovarian cancer cells by administration of compounds that inhibit PI kinase activity.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 37 and 38 were rejected as allegedly lacking adequate written description support in the specification. The rejection alleges that the application does not describe compounds other than LY294002 that inhibit PI-kinase activity such that a common structural feature of a PI-kinase inhibitory compounds was evident to the skilled artisan. Furthermore, the Examiner contends that the specification has not taught that inhibitors of PI kinase activity are generally effective in inhibiting ovarian cancer cell growth without also inhibiting growth of normal ovarian cells as well as other normal cells in the body.

Claims 37-39 were rejected as allegedly not enabled. The rejection alleges that the application does not provide sufficient guidance and working examples to enable the practitioner to make and use the claimed method without undue experimentation. The Examiner argues that additional research is still required to determine whether or not inhibition of PI-kinase will be effective for inhibiting ovarian cancer cell proliferation in a patient and that the outcome is unpredictable due to the complexity of the mechanisms involved in cancer. She further argues that the specification does not support the use of

PI inhibitors in general because there are innumerable kinases in the normal cell and that many of the possible PI kinase inhibitors would be expected to have harmful side effects.

In addition, the Examiner alleges that the submission of the Hu *et al.* paper with Applicants' previous response is insufficient as evidence to support the use of LY294002 as a therapeutic agent. The rejection argues that the publication cannot substitute for a declaration. She therefore requires that a Declaration under 37 C.F.R. §. 1.132 by at least one of the inventors be submitted that explains the relevant portions of the Hu *et al.* publication.

To the extent that the rejection applies to the amended claims, Applicants respectfully traverse both the written description rejection and the enablement rejection. Because the two rejections are closely related, they are addressed together.

PI3-kinase inhibitors are known and can be identified without undue experimentation

As explained above and in Applicants' response mailed October 1, 2001, the current invention is not a genus of PI3-kinase inhibitors. PI 3-kinase inhibitors are well known. For example, the compounds listed in the specification at page 24, lines 7-10 were known to inhibit PI3-kinase prior to Applicants' invention. Other inhibitors not explicitly recited in the specification were also known (*see, e.g.,* U.S. Patent No. 5,378,725, cited in the supplemental IDS submitted herewith, which discloses various wortmannin analogs). Moreover, PI3-kinase inhibitors can be identified using conventional assays (*see, e.g.,* the exemplary enzymatic assay described on page 34 of the specification and the assays described in U.S Patent No. 5,378,725 at column 11) and the effect on cancer cell proliferation assessed using well known techniques (*see, e.g.,* page 32, lines 3-17). Such assays can identify compounds that inhibit PI3 kinase via a variety of actions and may, in fact be structurally unrelated.

As noted in the MPEP at § 2163 (II)(A)(3)(a) "[W]hat is conventional or well known to one of ordinary skill in the art need not be disclosed in detail", citing *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802F.2d at 1384, 231 USPQ at 94. PI3 kinase and kinase inhibitors have been extensively studied, thus the state of the art is

advanced. Therefore, the specification, taken together with that which is known in the art, provides sufficient description and sufficient guidance for the skilled artisan to identify PI kinase inhibitors that inhibit pathologic proliferation of ovarian cancer cells without undue experimentation.

Description of safety and efficacy is not required

The Examiner also argues that the description requirements for treating a patient with a therapeutic agent are more complex than for a method of inhibiting growth of a cell *in vitro*. In both the written description and enablement rejections, she appears to be concerned about the effect of the compound on normal cells and argues that the specification has not described that inhibitors of PI kinase activity are generally effective at inhibiting ovarian cancer cell growth without also inhibiting growth of normal ovarian cells as well as other normal cells in the body. She concludes that the invention could therefore not be practiced without undue experimentation.

This aspect of the rejection appears to be concerned that the specification does not provide a description of compounds that inhibit ovarian cancer cell growth without causing potential side effects on non-cancerous cells and that one of skill in the art would therefore not be able to practice the invention because it would not be useful as a therapy. Applicants remind the Examiner that patentability of the claimed methods does not require that the invention is shown to be safe. As set forth in the MPEP at § 2107.01(V), the Office must confine its review to the statutory requirements of the patent law. It is improper for the Patent Office to request evidence of safety in the treatment of humans or regarding the degree of effectiveness. Applicants have disclosed that PI3-kinase inhibitors reduce the growth of ovarian cancer cells *in vitro* and *in vivo*. Applicants need not show the potential side effects, *i.e.*, present evidence of safety, nor demonstrate the efficacy of the treatment.

Lastly, submitted herewith is a Declaration by Joe Gray pursuant to 37 C.F.R. § 1.132, which explains the relevant portions of the Hu *et al.* reference.

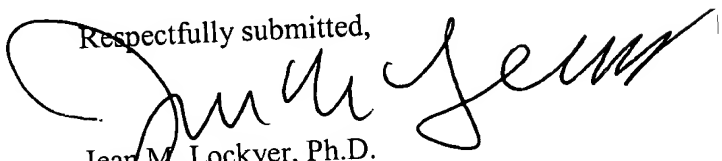
In summary, in view of the level of knowledge in the art and the requirements of patentability for the claimed methods, the specification both enables and fully describes Applicants' invention. Withdrawal of both the written description and enablement rejections is therefore respectfully requested.

CONCLUSION

Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at .

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

37. (three times amended) A method of inhibiting the pathological proliferation of ovarian cancer cells in a patient that has a population of ovarian cancer cells comprising cells in which 3q26 is amplified, the method comprising administering a therapeutically effective dose of an inhibitor of PI kinase to the patient, wherein the inhibitor inhibits PI kinase enzymatic activity.

38. (two times amended) The method of claim 37 36, wherein the inhibitor of PI kinase is a non-peptidic inhibitor of enzyme activity.

39. (amended) The method of claim 38, wherein the non-peptidic inhibitor is LY294002.